

Analgesic Effect of the Synthetic Cannabinoid CT-3 on Chronic Neuropathic Pain

A Randomized Controlled Trial

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A RECENT QUALITATIVE SYSTEMATIC review of the effectiveness of cannabinoids in the management of pain advised against their widespread introduction into clinical practice because of limited relative efficacy in acute pain and common adverse effects.¹ However, it was suggested that cannabinoids may have some beneficial effect in spasticity and in neuropathic pain, for which a therapeutic need is greater than in postoperative pain. In addition, the authors stated that new safe and effective agonists at the cannabinoid receptors may dissociate therapeutic effects from psychotropic effects, which makes randomized comparisons in neuropathic pain and spasticity worthwhile.¹

1',1'-Dimethylheptyl- Δ^8 -tetrahydrocannabinol-11-oic acid (CT-3) potentially possesses the efficacy to treat neuropathic pain and spasticity without the psychotropic liabilities of cannabis. CT-3 is a synthetic analog of tetrahydrocannabinol (THC)-11-oic acid, one of the endogenous transformation products of THC, in which a dimethylheptyl side chain is substituted for the pentyl side chain.² In preclinical studies, CT-3 was found to be a potent anti-inflammatory, analgesic, and antiallodynic agent

Context 1',1'-Dimethylheptyl- Δ^8 -tetrahydrocannabinol-11-oic acid (CT-3), a potent analog of THC-11-oic acid, produces marked antiallodynic and analgesic effects in animals without evoking the typical effects described in models of cannabinoids. Therefore, CT-3 may be an effective analgesic for poorly controlled resistant neuropathic pain.

Objective To examine the analgesic efficacy and safety of CT-3 in chronic neuropathic pain in humans.

Design and Setting Randomized, placebo-controlled, double-blind crossover trial conducted in Germany from May-September 2002.

Participants Twenty-one patients (8 women and 13 men) aged 29 to 65 years (mean, 51 years) who had a clinical presentation and examination consistent with chronic neuropathic pain (for at least 6 months) with hyperalgesia (n=21) and allodynia (n=7).

Interventions Patients were randomized to two 7-day treatment orders in a crossover design. Two daily doses of CT-3 (four 10-mg capsules per day) or identical placebo capsules were given during the first 4 days and 8 capsules per day were given in 2 daily doses in the following 3 days. After a washout and baseline period of 1 week each, patients crossed over to the second 7-day treatment period.

Main Outcome Measures Visual analog scale (VAS) and verbal rating scale scores for pain; vital sign, hematologic and blood chemistry, and electrocardiogram measurements; scores on the Trail-Making Test and the Addiction Research Center Inventory-Marijuana scale; and adverse effects.

Results The mean differences over time for the VAS values in the CT-3-placebo sequence measured 3 hours after intake of study drug differed significantly from those in the placebo-CT-3 sequence (mean [SD], -11.54 [14.16] vs 9.86 [21.43]; $P=.02$). Eight hours after intake of the drug, the pain scale differences between groups were less marked. No dose response was observed. Adverse effects, mainly transient dry mouth and tiredness, were reported significantly more often during CT-3 treatment (mean [SD] difference, -0.67 [0.50] for CT-3-placebo sequence vs 0.10 [0.74] for placebo-CT-3 sequence; $P=.02$). There were no significant differences with respect to vital signs, blood tests, electrocardiogram, Trail-Making Test, and Addiction Research Center Inventory-Marijuana scale. No carryover or period effects were observed except on the Trail-Making Test.

Conclusions In this preliminary study, CT-3 was effective in reducing chronic neuropathic pain compared with placebo. No major adverse effects were observed.

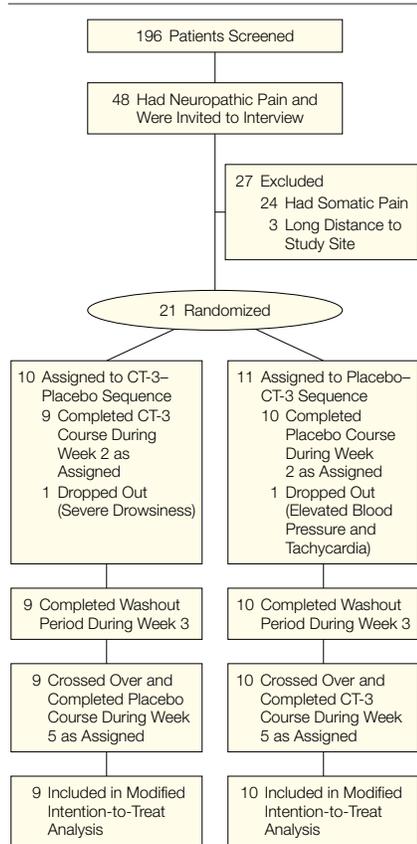
JAMA. 2003;290:1757-1762

www.jama.com

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Financial Disclosure: Dr Burstein is the inventor listed on the patents underlying the technology described in this article.

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Figure 1. Flow of Participants

CT-3 indicates 1',1'-dimethylheptyl- Δ^8 -tetrahydrocannabinol-11-oic acid.

without psychoactive properties.² Although the exact neurobiological mechanism of action is still unclear, some evidence exists that apart from the known cannabinoid receptors (CB1 and CB2), 1 or more undiscovered cannabinoid receptors are involved in mediating the analgesic and anti-inflammatory effects of CT-3.² In addition, other studies suggest possible postreceptor mechanisms, including inhibition of eicosanoid synthesis and down-regulation of cyclooxygenase 2.³ Recent data suggest that the peroxisome proliferator-activated receptor γ (PPAR γ) may serve as an intracellular receptor for CT-3.⁴ The activation of PPAR γ is directly linked to anti-inflammatory and antitumor processes.⁴

The aim of this preliminary study was to examine the analgesic efficacy and safety of CT-3 in chronic neuropathic pain.

METHODS

Patients

Newspaper advertisement led to 196 telephone contacts. Only 48 of the contacted individuals appeared to have neuropathic pain and were invited to an interview. Among these, 24 had both neuropathic and somatic pain and were therefore excluded. Three patients were denied participation because of the long distance from their homes to the study site. Inclusion criteria were pain for at least 6 months, stable levels of pain medications for at least 2 months, age 18 to 65 years, and consent to participate in the study and follow study procedures. Concomitant pain-relieving medications allowed were antipyretic and opioid analgesics, flupirtine, anticonvulsants, and antidepressants. Not allowed were *N*-methyl-D-aspartate receptor antagonists and cannabinoids. Other specific exclusion criteria were severe organic or psychiatric disease, pregnancy or attempting to conceive, lactation, use of any investigational drug within 30 days prior to first dose of study drug, and non-German speaking. The selected 21 patients (8 women and 13 men) aged 29 to 65 years (mean, 51 years) had a clinical presentation and examination consistent with chronic neuropathic pain with hyperalgesia (n=21) and allodynia (n=7).

Diagnoses in the study group included neuropathic pain of the left arm (n=5) and right arm (n=1) due to traumatic cervicobrachial plexus lesions, mainly at C5 to C8; neuropathic facial pain (n=3) due to traumatic lesions of the left maxillary nerve, left trigeminal nerve, and mental nerve bilaterally; neuropathic pain behind the left ear (n=1) due to traumatic lesion of the left great auricular nerve; neuropathic pain of the left forearm and hand (n=1) due to traumatic lesion of the left radial nerve; neuropathic pain in the left leg (n=3) and right leg (n=1) due to lumbar disk protrusion or intraspinal scar tissue after lumbar disk surgery, mainly at L5/S1; neuropathic pain in one or both of the legs (n=3) due to traumatic spinal cord lesions at L1; neuropathic pain of the sole of the left foot due to compression of the tibial nerve (tarsal tunnel syndrome)

(n=1); neuropathic whole-body pain below the shoulders due to tethered cord syndrome after surgical removal of an intrathecal ependymoma at C4 to T1 (n=1); and neuropathic left facial pain (n=1) of unknown cause. The study protocol was approved by the Hannover Medical School institutional review board, Hannover, Germany, and the German Federal Institute for Drugs and Medical Devices, and written informed consent was obtained from all patients.

Study Design and Assessment

This randomized, double-blind, placebo-controlled crossover study was conducted from May-September 2002 and lasted 5 weeks (FIGURE 1). Weeks 1 and 4 were baseline weeks, weeks 2 and 5 were intervention weeks, and week 3 was a washout period. Patients were randomized either to CT-3 or to placebo. During the first intervention week, 2 daily doses were given (four 10-mg CT-3 capsules per day) during the first 4 days and 8 capsules per day in 2 daily doses during the following 3 days; placebo was administered in the same amounts and with the same appearance of capsules. After a washout period of 1 week, the patients crossed over to the alternate group for another 7-day treatment period. For measurement of pain, during each baseline week and each intervention week, patients completed a visual analog scale (VAS) and a verbal rating scale (VRS) twice per day (11 AM and 4 PM, 3 and 8 hours after the morning dose, respectively) for 1 week and recorded the values in a patient diary.

The VAS consisted of a 100-mm horizontal line with 2 end points labeled as 0 (no pain) and 100 (worst pain ever). The VRS consisted of a series of verbal pain descriptors ordered from least to most intense (none=0, weak=1, moderate=2, severe=3, and excruciating=4).

The CT-3 was produced by Creapharm, Le Haillan, France. The drug substance was mixed with an appropriate amount of lactose and filled into No. 2 hard gelatin capsules at 10 mg each. Placebo capsules were identical in all respects except for the absence of CT-3. Randomization, labeling, and packaging

ing in high-density polyethylene bottles were performed at Creapharm, which dispensed the study medication under blinded conditions through computer-based randomization.

Study investigators were blinded to the randomization method. All study bottles were labeled with numbers from 1 to 21 pertaining to each of the 21 patients. Each study day (14 in all) was indicated on the bottles, each of which contained either 4 or 8 capsules. Altogether, 21 sets of 14 bottles each were numbered. According to the sequence of their inclusion, participants were assigned consecutive numbers that were then correlated with the numbers on the bottles. All persons involved in the study were unaware of which treatment was administered. Assessments were performed by graduate medical students and the medication was dispensed by the attending physicians. Treatment assignment codes were not available to investigators until all patients completed the study and the data had been entered.

In addition, the baseline screening evaluation included a review of concomitant pain medication, which was allowed if patients had been receiving stable doses for at least 2 months prior to entry into the study. A neurological examination, vital sign measurements, an electrocardiogram, and hematologic and blood chemistry studies (chloride, sodium, potassium, creatinine, total bilirubin, alkaline phosphatase, γ -glutamyl transferase, alanine aminotransferase, aspartate aminotransferase, and whole blood cell count) were performed, and the Trail-Making Test (TMT) and Addiction Research Center Inventory–Marijuana (ARCI-M) scale were also used in the baseline assessment.

To determine impairment of cognition, part B of the TMT was used, consisting of a 1-page worksheet of scattered, circled numbers and letters. Patients were asked to connect consecutively numbered circles and lettered circles, alternating between numbers and letters, without lifting the pencil from the page, in as little time as possible. The test was scored by time to completion and number of errors.⁵

Subjective drug effects were determined using the 12-item ARCI-M scale, which derives from a 53-item version of the ARCI⁶ plus 4 items specific to marijuana.⁷ These 4 items are “I have difficulty in remembering,” “My mouth feels very dry,” “I notice that my heart is beating faster,” and “My thoughts seem to come and go.” The items are answered as true or false, and each true response is scored as 1 point.

Response was assessed with a pain diary in which the patients completed the VAS and VRS at 11 AM and 4 PM at each day, 3 and 8 hours after the morning intake of the capsules, respectively. In addition, spontaneous adverse events were collected in the diaries. On the first and last days of the treatment week, the TMT and ARCI-M scale were administered along with an electrocardiogram. On the first, fifth, and last days of the treatment week, hematologic and blood chemistry measurements were taken. Vital signs were measured daily. All measurements were performed at least 2 hours after intake of the morning dose of the study drug. Furthermore, at each appointment, compliance was assessed by collection of the study medication bottles. Patients were not asked to guess which treatment they had received during each period; some patients commented on this point but no responses were made regarding these comments.

Statistical Analysis

We assumed that there would be no carryover effect after the washout period of 1 week (week 3). The α level was .05 with a power of 90%. Using a 2-sided test with a 2-period crossover design resulted in the need to enroll a total of 21 patients.

Results are presented as means (SDs). Demographic data, duration of pain, and pain intensity were analyzed with the unpaired *t* test; sex, type of neuropathic pain, presence of allodynia, and regular use of concomitant pain medication were measured as frequency data. Categorical data were analyzed with the Fisher exact test. Pain scores, the TMT, the ARCI-M scale, and vital signs were computed for treatment effects, period effects, and carryover effects by the method

reported by Hills and Armitage⁸ for 2-period crossover clinical trials. These quantitative data were analyzed using the unpaired *t* test to evaluate between-group differences in the 2 sequence groups. For the analysis of pain-reducing effects of the intervention period, the differences between each intervention week's results and the corresponding baseline week results (week 2 – week 1 and week 5 – week 4) were computed. For the analysis of the difference over time, the difference (week 2 – week 1) – (week 5 – week 4) was computed. Statistical significance was determined as $P < .05$. Analyses were conducted using SPSS, version 11.0 (SPSS Inc, Chicago, Ill).

RESULTS

Patient Characteristics and Disposition

Of the 21 patients, 10 were randomly assigned to receive CT-3 first then placebo, and 11 were assigned to receive placebo first, then CT-3 (Figure 1). The 2 groups were well balanced with respect to age, sex, duration of pain, type of neuropathic pain, and regular use of concomitant analgesics (opioids, anticonvulsants, antidepressants, antipyretic analgesics), and mainly central-acting compounds (diazepam and zolpidem) (TABLE). In 10 patients, the following pain medications and dosages were in regular use: 1 patient each took metamizol, 1000 mg every 6 hours; metamizol, 750 mg every 4 hours; controlled-release morphine, 90 mg, and diazepam, 10 mg, every 24 hours; controlled-release formulation of oxycodone, 100 mg every 6 hours; zolpidem, 10 mg every 4 hours (abusively); doxepin, 25 mg in the evening, imipramine, 20 mg twice per day, and sublingual buprenorphine every 6 hours; controlled-release tramadol, 100 mg every 8 hours; celecoxib and citalopram once per day, flupirtine, 100 mg every 6 hours, and gabapentin, 200 mg every 8 hours; controlled-release tramadol, 100 mg every 12 hours; and controlled-release tilidine/naloxone, 100/8 mg in the morning, amitriptyline, 50 mg in the evening, and gabapentin, 300 mg every 8 hours.

At both baseline weeks, mean (SD) pain levels on the VAS were between

56.00 (20.93) and 68.07 (14.25) for the entire group. With the exception of the 4 PM VAS assessment in week 1, both sequence groups differed significantly in their baseline VAS scores (11 AM in week 1, $P = .03$; 11 AM in week 4, $P = .002$; and 4 PM in week 4, $P = .03$) (Table 1).

Two patients dropped out on the second day of the first intervention week.

Therefore, their small amount of data was not considered for further analysis or imputation methods, which led to a modified intention-to-treat analysis. One of these patients, a placebo patient with no history of cardiovascular disease, experienced elevated blood pressure (214/105 mm Hg) and tachycardia (122/min). The patient was re-

ferred to a cardiologist. One patient treated with CT-3 experienced severe drowsiness, which interfered with his work. This patient was also taking a controlled-release preparation of oxycodone, 100 mg every 6 hours.

Pain Measurements

Morning results (3 hours after intake of the study drug) of the CT-3 intervention weeks (weeks 2 and 5) showed significant reduction in pain scores and a strong tendency toward significant pain reduction as measured by mean (SD) VAS and VRS differences over time ([week 2 – week 1] – [week 5 – week 4]), respectively. For the CT-3–placebo sequence, the difference in VAS scores for week 2 – week 1 was –13.07 (13.76), for week 5 – week 4 was –1.52 (12.98), and the difference over time was –11.54 (14.16). For the placebo–CT-3 sequence, the difference in VAS scores for week 2 – week 1 was –3.14 (13.11), for week 5 – week 4 was –13.00 (22.14), and the difference over time was 9.86 (21.43); $P = .02$ by independent t test (FIGURE 2A). For the CT-3–placebo sequence, the difference in VRS scores for week 2 – week 1 was –0.36 (0.47), for week 5 – week 4 was –0.11 (0.40), and the difference over time was –0.25 (0.49). For the placebo–CT-3 sequence, the difference in VRS scores for week 2 – week 1 was –0.19 (0.55), for week 5 – week 4 was –0.61 (1.01), and the difference over time was 0.42 (1.05); $P = .10$ by independent t test (Figure 2B).

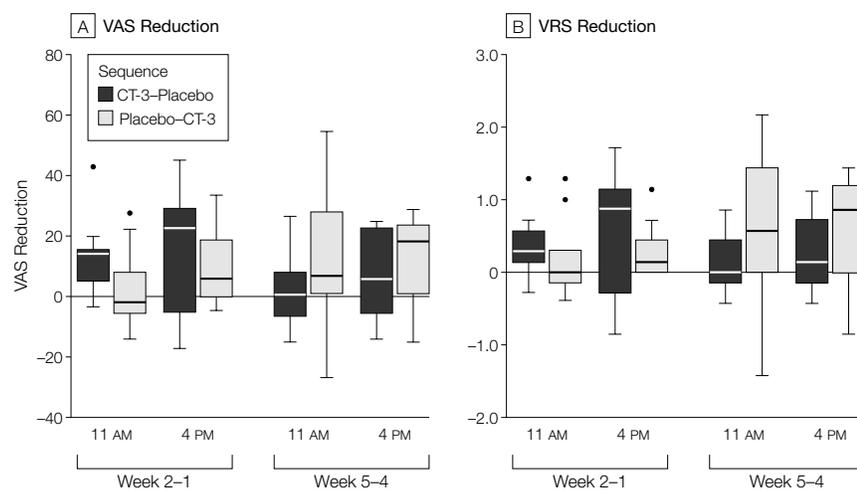
The afternoon results (8 hours after morning intake of the study drug) showed less marked effects. For the CT-3–placebo sequence, the difference in VAS scores for week 2 – week 1 was –15.56 (23.38), for week 5 – week 4 was –5.91 (14.82), and the difference over time was –9.65 (29.15). For the placebo–CT-3 sequence, the difference in VAS scores for week 2 – week 1 was –8.26 (11.39), for week 5 – week 4 was –12.39 (14.48), and for the difference over time was 4.13 (10.43); $P = .21$ by independent t test (Figure 2A). For the CT-3–placebo sequence, the difference in VRS scores for week 2 – week 1 was –0.57 (0.95), for week 5 – week 4 was –0.25

Table. Demographic Characteristics of the Study Groups*

Characteristics	Total (N = 21)	CT-3–Placebo Sequence (n = 10)	Placebo–CT-3 Sequence (n = 11)
Age, y	50.86 (11.69)	51.50 (9.91)	50.27 (13.56)
Sex, male/female, No.	13/8	6/4	7/4
Type of neuropathic pain, peripheral/central, No.	17/4	8/2	9/2
Allodynia, No.	7	4	3
Intensity of pain on VAS†			
Week 1, 11 AM‡	56.00 (20.93)	45.30 (17.70)	65.63 (19.49)
Week 1, 4 PM	64.63 (17.62)	58.14 (15.05)	70.47 (18.42)
Week 4, 11 AM‡	60.00 (17.63)	48.16 (11.15)	70.66 (15.64)
Week 4, 4 PM‡	68.07 (14.25)	60.73 (6.55)	74.67 (16.30)
Duration of pain, y	11.48 (7.15)	12.80 (6.75)	10.27 (7.62)
Regular use of concomitant analgesics, yes/no, No.§	10/11	5/5	5/6

Abbreviations: CT-3, 1',1'-dimethylheptyl- Δ^8 -tetrahydrocannabinol-11-oic acid; VAS, visual analog scale.
 *Data are expressed as mean (SD) unless otherwise noted.
 †The VAS consisted of a 100-mm horizontal line with 2 end points labeled as 0 (no pain) and 100 (worst pain ever).
 ‡ $P < .05$ for the intergroup differences between the CT-3–placebo and placebo–CT-3 sequences.
 §Concomitant analgesics included opioids, anticonvulsants, antidepressants, antipyretic analgesics, flupirtine, and mainly central-acting compounds (diazepam and zolpidem).

Figure 2. Effect of CT-3 on Reduction in VAS and VRS Scores



CT-3 indicates 1',1'-dimethylheptyl- Δ^8 -tetrahydrocannabinol-11-oic acid; VAS, visual analog scale (range, 1–100); VRS, verbal rating scale (range, 0–4). The figure shows the effect of CT-3 on reduction (week 2 – week 1 and week 5 – week 4) in VAS and VRS scores. The CT-3–placebo sequence group received CT-3 in week 2 and placebo in week 5. The placebo–CT-3 sequence group received CT-3 in week 5 and placebo in week 2. Medians are represented by horizontal bars, interquartile ranges by boxes, ranges by error bars, and extreme values by circles. For differences over time, the reduction in the VAS scores was significantly different ($P = .02$) in the 11 AM measurements. No significant differences over time were observed in the VRS scores.

(0.55), and the difference over time was -0.32 (1.13). For the placebo–CT-3 sequence, the difference in VRS scores for week 2 – week 1 was -0.29 (0.38), for week 5 – week 4 was -0.62 (0.74), and the difference over time was 0.33 (0.66); $P = .14$ by independent t test (Figure 2B).

The effect size for CT-3 was somewhat greater in the CT-3–placebo sequence, with less pain intensity at baseline (Table 1) than in the placebo–CT-3 sequence. The VAS and VRS reductions in the CT-3–placebo sequence at 11 AM were 28.84% and 18.89% and at 4 PM were 26.75% and 23.76%, respectively. In contrast, the VAS and VRS reductions in the placebo–CT-3 sequence at 11 AM were 18.40% and 21.49% and at 4 PM were 16.59% and 20.13%, respectively.

All patients used the opportunity to increase the dosage on day 5 of each intervention week, but no significant dose response or increase in adverse events was observed. No carryover or period effects were observed.

Adverse Events

Reported adverse events were mainly tiredness and dry mouth but also included limited power of concentration, dizziness, sweating, and more pain. These adverse events were reported significantly more often when CT-3 was administered (mean [SD] difference over time, -0.67 [0.50] for CT-3–placebo sequence vs 0.10 [0.74] for placebo–CT-3 sequence; $P = .02$ by independent t test). In the CT-3–placebo sequence, during the CT-3 period, 6 of 9 patients reported such adverse events vs 0 of 9 in the placebo period. In the placebo–CT-3 sequence, 6 of 10 reported adverse events in the CT-3 period vs 5 of 10 in the placebo period. Neither the TMT nor the ARCI-M scale scores showed significant differences over time between the 2 treatment groups. The mean (SD) difference over time for the TMT score was 35.89 (112.80) seconds in the CT-3–placebo sequence and was 3.15 (63.45) seconds in the placebo–CT-3 sequence. On the ARCI-M, the mean (SD) difference over time for the number of items answered as true was

-0.67 (3.61) in the CT-3–placebo sequence and was 0.22 (2.59) in the placebo–CT-3 sequence. However, there was a carryover effect observed with the TMT ($P = .03$). No significant differences were found with respect to changes in vital signs, weight, temperature, electrocardiographic findings, or hematologic and blood chemistry studies.

COMMENT

Neuropathic Pain

Understanding of the etiology and pathophysiology of neuropathic pain has increased over the past few years, particularly on a molecular and genetic level. Activation of intracellular signal transduction cascades results in changes of receptor and ionic channel function, which may remain active following initial trauma (long-term potentiation).⁹ There is still much to be understood between the etiological findings and the therapeutic possibilities.

Neuropathic pain cannot be totally eliminated by means of preventive measures, and there is no completely effective medication available with an acceptable therapeutic ratio of efficacy to safety. Apart from inhibiting sodium ion channels (by use of anticonvulsants or local anesthetics) and assisting endogenous noradrenergic and serotonergic mechanisms (by use of antidepressants), an increasing number of *N*-methyl-D-aspartate receptor antagonists have been introduced in the past few years. Many of these have produced favorable therapeutic results.¹⁰ Nevertheless, their use is restricted by a poor adverse effect profile; thus, there is a need for effective alternatives with acceptable adverse effect profiles.

Cannabinoids for Chronic Pain

Preclinical studies have shown that cannabinoids reduce the hyperalgesia and allodynia associated with formalin, capsaicin, carrageenan, nerve injury, and visceral persistent pain¹¹; therefore, exogenous cannabis or cannabinoids may work as an analgesic in poorly controlled neuropathic pain. In addition, humans have cannabinoid receptors in the central and peripheral nervous sys-

tem,¹² although the functions of these receptors and their endogenous ligands remain unclear.

Although a large number of case reports and letters suggest the benefits of cannabis or cannabinoids in chronic pain and other conditions, there is little research-based evidence.¹³ Oral THC, 5 to 20 mg, was found to have an analgesic effect compared with placebo in 10 patients with pain related to advanced cancer.¹⁴ In this study, a dose-response relationship was shown for analgesia and adverse effects. In a further study by the same research group, THC, 10 mg, was found to be equipotent to codeine, 60 mg, and THC, 20 mg, was equipotent to codeine, 120 mg, but the higher dose was associated with unacceptable adverse effects.¹⁵ In a patient with neuropathic pain and spasticity secondary to a spinal cord ependymoma, THC, 5 mg, and codeine, 50 mg, were equianalgesic, and both were superior to placebo. Only THC, however, had a beneficial effect on spasticity.¹⁶

Tetrahydrocannabinol has psychological adverse effects including psychomotor and cognitive impairment, anxiety and panic attacks, and acute psychosis and paranoia¹⁷ and adverse physical effects including dry mouth, blurred vision, palpitations, tachycardia, and postural hypotension¹⁸ in doses as low as 10 to 20 mg.

Pharmacokinetics and Pain Reduction

CT-3, a synthetic analog of THC-11-oic acid, has been shown in animal tests to have potent anti-inflammatory, analgesic, and antiallodynic effects without psychoactive properties.² The following findings recently have been corroborated: The absence of psychoactive properties was confirmed in 24 human volunteers with a dose of up to 10 mg of CT-3 (S.B., unpublished data, 2001). After a single oral administration of CT-3 in 6 human volunteers, the time to highest plasma concentration (t_{max}) was reached in most participants 1 or 2 hours after absorption from the empty gastrointestinal tract, but some participants had a delayed t_{max} of 4 to 5 hours. Furthermore, plasma

concentrations of CT-3 demonstrated a strong linear relationship to dose. The peak plasma concentrations of CT-3 increased in ratios of 3.7, 6.2, and 12.6 for CT-3 doses of 3, 6, and 10 mg compared with 1 mg. Similarly, the extrapolated area under the curve (AUC_{0-8}) of CT-3 increased in ratios 3.6, 5.5, and 11.0, respectively. Moreover, in rats and dogs, concentration of CT-3 in plasma reached peak levels 1.5 to 6 hours after dosing and declined thereafter with apparent half-lives of 4 to 13 hours, although longer half-lives may have occurred in some female dogs at high doses.

Our investigation showed that CT-3, given in daily doses of 40 and 80 mg, is more effective than placebo for neuropathic pain, with greater pain-reducing effects at 3 hours after intake than at 8 hours. These findings may confirm the pharmacokinetic data regarding CT-3 known in humans and animals, with main clinical effects observed in the first 6 hours after intake of the drug. The observation of prolonged effects in animal studies² could not be confirmed statistically in this study; nevertheless, even 8 hours after intake of the drug, there was a tendency toward more pain reduction during the CT-3 intervention. Considering the small sample size, this result may have more weight than the statistical analysis indicates. Furthermore, the amount of pain reduction by the study drug was generally more marked in patients with lower baseline pain levels. This finding may be an indication of a limitation of the pain-reducing efficiency of the compound and a general observation that mild pain is easier to reduce than severe pain. Elevation of the dose increased neither pain reduction nor adverse events, which may be a strong argument for 20 mg as a single dose for this compound.

Adverse Events

CT-3 appeared to be free of psychoactive properties as measured by the TMT and the ARCI-M scale, though the assessment of the TMT was restricted by the observed carryover effect. The TMT is often used for screening for cognitive impairment in marijuana abusers.¹⁹ We

restricted the use of the TMT to part B because only part B is a general indicator for brain dysfunction. Its cognitive demands include visual scanning, visual-motor coordination, and visual-spatial ability adequate enough to understand on an ongoing basis the alternating pattern of numbers and letters.⁵ In addition, in terms of construct validity, there are several factors that make part B more difficult.²⁰ The ARCI-M scale was used as an outcome measure for subjective effects because in previous studies of THC and marijuana,^{7,21} increases on the ARCI-M scale were observed together with prototypic subjective experiences with marijuana use.

In our study, tiredness was the main adverse psychological event and dry mouth was the main adverse physical effect; major physical adverse events were not observed. Only 1 CT-3-related dropout occurred (because of severe drowsiness) when CT-3 was used in conjunction with a high dosage of oxycodone (400 mg/d).

CONCLUSION

Because this preliminary study showed the effectiveness of CT-3 in neuropathic pain and did not find clinically relevant adverse events, and because in animal studies no signs of strong dependency after withdrawal of the drug have been found,² further clinical studies with CT-3 are warranted. Future studies with this agent should be conducted over weeks or months and should consider a shorter dosing interval, such as 6 to 8 hours.

Author Contributions: Dr Karst, as principal investigator, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Karst, Salim, Conrad, Schneider.
Acquisition of data: Karst, Salim, Burstein, Conrad.
Analysis and interpretation of data: Karst, Conrad, Hoy, Schneider.
Drafting of the manuscript: Karst, Salim, Hoy.
Critical revision of the manuscript for important intellectual content: Karst, Salim, Burstein, Hoy, Schneider.
Statistical expertise: Karst, Conrad, Hoy.
Obtained funding: Karst, Schneider.
Administrative, technical, or material support: Karst, Salim, Conrad.
Study supervision: Karst, Conrad, Schneider.
Funding/Support: This study was supported by a research grant from Atlantic Technology Ventures Inc

(which paid for the CT-3 used in this study) and Indevus Pharmaceuticals Inc.

Role of the Sponsor: Neither funding source was involved in the design and conduct of the study; the collection, analysis, and interpretation of the data; or the preparation, review, and approval of the manuscript.
Acknowledgment: We acknowledge graduate medical students Gerrit Ahrenstorff, Michael Al-Ghazaf, Kevin Bullert, Christine Geffcken, and Gisa Kuehn as well as Gaby Huwald, RN, for help with the study execution.

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